REMARKS

Claims 1-12, 14 and 16-26 are currently under examination. For convenience, a copy of the claims under examination is provided in Appendix A, attached hereto.

The amendments to the specification add no new matter.

The amendment at paragraph 1, lines 8-12 splits the original paragraph into two paragraphs. The first paragraph in the specification has been amended to refer to both of the parent applications. Support for incorporating the parent applications by reference is found, *e.g.,* in the application transmittal sheet filed with the application, relating to parent Application No. 09/071,672, and page 32, lines 1-2 of the specification. The second paragraph was amended to provide the application number for U.S. Provisional Patent Application "Recombinant Anti-Tumor RNAse," filed March 27, 1998 (Attorney Docket No. 15280-343000), which was co-pending with the parent application at the time of filing.

For convenience, the objections/rejections will be addressed in the order set forth in the January 28, 2003 Office Action.

Priority

Applicants note that the priority claim to parent application 09/071,672 was provided in the Application Data Sheet filed with the application. However, the first paragraph has been amended to update and complete the priority information.

Objections to the specification

The passages noted by the Examiner have been amended to address the objections. Please note that in addition to correcting the paragraph on page 29, lines 7-15 to delete the "[]" sign, this paragraph was also amended to insert the apostrophe in "Burkitt's".

Rejection under 35 U.S.C. § 112, second paragraph

Claim 14 was rejected as allegedly indefinite in the recitation of "recombinant fusion". Applicants respectfully traverse. The meaning of the term is readily determined from the disclosure in the specification. "Recombinant fusion" refers to a cytotoxic reagent that is produced as a recombinant protein in which the onc protein moiety is linked to the antibody moiety. For example, on page 18, beginning on line 32 through page 19, line 18, the specification teaches that recombinant DNA techniques can be used to link the recombinant onc protein and the antibody and thus the immunotoxin can comprise a fused protein (examples of which are also provided at the passage cited). Further, the specification defines a recombinant protein (*see, e.g.,* page 11, lines 26-32) and provides a definition of the term "joined" (*e.g.,* at page 8, lines 7-11), which teaches that the moieities comprised by the immunotoxin can be joined by recombinant fusion. Accordingly, the term is clear. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 6-12, 14, 16, 18 and 21-26 were rejected as allegedly lacking adequate written description and as allegedly not enabled. The rejections allege that the specification does not describe the full scope of the claimed genus, nor does it provide sufficient guidance to make selective cytotoxic reagents comprising an onc protein derived from any species other than *Rana pipiens*. Applicants respectfully traverse both rejections. The specification is fully compliant with the written description requirement and enables the scope of the claimed invention.

<u>The claimed immunotoxins are described in the specification</u>

The rejection alleges that the claimed genus of onc proteins, including proteins other than those from *Rana pipiens*, is not described in the specification. In particular, the Examiner quotes the Federal Circuit in the *University of California v. Eli*

Lilly and Co. 43 USPQ 2d 1398 (Fed. Cir. 1997), noting that a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs that fall within the scope of the genus or recitation of structural features common to the genus, which feature constitute a substantial portion of the genus. The rejection appears to suggest that the specification provides neither structural charactertistics of onc proteins nor representative species of onc proteins for use in the invention. Applicants disagree with the Examiner's conclusions and application of the selected passage of *Lilly* to the instant invention. First, in *Lilly*, there was no information in the specification that related to the actual sequence of the claimed human insulin cDNA. Accordingly, no physical or structural characteristics of the claimed cDNA was provided. The Court concluded that "naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material." (*Lilly* at page 1399, emphasis added). In that context, the "human insulin cDNA" designation recited in the claims was found to refer to a function and not convey information about the identity of the molecule.

In contrast, the tem "onc protein" recited in the instant claims *does* convey information concerning the identity of the element. Applicants have defined an onc protein in the specification (*see*, *e.g.*, page 9, lines 10-19) as an RNase A derived from *Rana pipiens*. The specification also defines native and recombinant onc proteins and additionally sets forth specific citations from the art, which are incorporated by reference, that teach preferred recombinant onc proteins (*see, e.g.*, page 9, lines 15-17). The written description requirement does not demand a detailed description of that which is known to one of ordinary skill in the art. The Revised Written Description Examination Guidelines, Federal Register, Vol. 66, No.4, 1099, Jan. 5, 2001, state that

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then

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the adequate description requirement is met.
(page 1106)
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Thus, the term "onc protein" refers to structures known in the art. As such, the term conveys the required information. Accordingly, in view of the knowledge in the art and the definitions provided in the specification, the disclosure meets the written description requirement. Applicants therefore respectfully request withdrawal of the rejection.

The specification fully enables the claimed compositions

In the Office Action the Examiner acknowledges that the specification is enabled for onc proteins having the amino acid sequences shown in SEQ ID NOs: 1 and 3; however she then alleges that the specification does not reasonably provide enablement for "any onc protein other than those derived from *Rana pipiens*". Applicants respectfully traverse this rejection.

As noted above, Applicants have defined an onc protein in the specification (*see, e.g.*, page 9, lines 10-19) as an RNase A derived from *Rana pipiens*, defined native and recombinant onc proteins, and provided guidance for identifying preferred recombinant onc proteins. In determining whether undue experimentation is required to practice the claimed invention, factors such as the amount of guidance presented in the specification and the presence of working examples must be considered (*see*, *Ex Parte Forman*, 230 USPQ 546 (Bd. Patent App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Circ 1988). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should precede" (*see, Wands,* 8 USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Thus, Applicants are not required to disclose every conceivable onc protein for the disclosure to be enabling.

Applicants have offered specific guidance for identifying and making a surprisingly effective cytotoxic reagent (an onc protein joined to an antibody to a B cell surface marker) to be used as claimed. (*See, e.g.*, the Examples). Further, Applicants have provided information for the skilled artisan to identify preferred embodiments of onc proteins, *i.e.*, *Rana pipiens* RNase A proteins. Lastly, a Declaration under 37 C.F.R. § 1.132, which was submitted in parent application 09/071,672, and is further explained below, provides additional evidence that the specification teaches how to make and use compositions with the claimed properties. Thus, in view of the teachings in the specification taken in conjunction with that which is known to those of skill in the art, no undue experimentation is required to make and use the cytotoxic reagents of the invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 102(e)

Claims 1, 6, 9-11, 14, 16, 18, 21, 22, 25, and 26 were rejected as allegedly anticipated by Goldenberg (US Patent No. 5,083,477). The rejection alleges that the reference teaches a method of killing B cells in which the monoclonal antibodies LL1 and LL2 that bind to CD74 and CD22 were conjugated to the RNAse EDN or onconase, and that the onc cytotoxic reagent is at least 100 times more cytotoxic compared to the same antibody attached to EDN.

In parent application 09/071,672, Applicants submitted a Declaration of Inventorship under 37 C.F.R. § 1.132 by David M. Goldenberg. Applicants provide herewith a copy of the Declaration, attached as Appendix B, which states that he was not the sole inventor of the subject matter relating to onconase immunocojugates described in Example 2, Example 8, and Table 2 of the cited reference. The Declaration further states that the inventors of the subject matter are the inventors of the current application. Thus, the invention was not described in a patent granted on an application for patent by another before the invention thereof by the present applicants. Withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-12, 14, and 16-26 were rejected as allegedly obvious over Rybak *et al.* (U.S. Patent NO. 5,840,840) and/or Ghetie *et al.*, in view of a number of different cited references (Rybak *et al.*, in *Tumor Targeting*, 1995; Rybak *et al.*, in *PNAS*, 1992; Goldenberg, *supra*; Sausville *et al.*, in *Blood*; Janeway, *et al.*, in *Immunobiology*; and Huston, *et al.* in *PNAS*). First, Applicants note that the Declaration of Inventorship that removes Goldenberg as prior art under 35 U.S.C. § 102(e), also removes Goldenberg as a prior art reference under 35 U.S.C. § 103 (*see, e.g.*, MPEP § 715.01(c)). With regards to the other aspects of the rejections, Applicants respectfully traverse. Further, in order to expedite prosecution, Applicants also provide a copy of a Declaration under Rule 132 by Dr. Susanna Rybak, attached as Appendix C, that was submitted in parent application 09/071,672, which Declaration attests to the surprising results obtained with the cytotoxic reagents of the present invention.

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate that: (1) there is some suggestion or motivation to modify the reference or combine the reference teachings; (2) there is a reasonable expectation of success: and (3) the prior art references suggest all the claim limitations. *See, e.g.*, MPEP § 2143. The present application teaches that a reagent comprising an onc protein linked to an antibody to a B cell surface marker, such as CD22, exhibits markedly enhanced cytotoxicity relative to a human RNase linked to the same antibody. The cited art does not specifically identify the combination of elements and the surprising results seen with this particular combination.

The '840 patent refers to <u>many</u> RNase proteins as well as RNase A from *Rana pipiens*, and also refers to <u>many</u> recognition moieties. The patent, however, does not specifically suggest the immunoconjugate combination claimed here nor does it suggest the striking surprising results obtained with the particular combination. Further, the '840 patent does not specifically disclose LL2-onc conjugates, nor does it disclose

that these conjugates are markedly more cytotoxic than immunoconjugates containing a human RNase joined to LL2.

Ghetie *et al.* disclose an antibody to a CD22 cell surface marker conjugated to ricin, but do not teach or suggest an onc protein. Similarly, Sausville teach an antibody to a CD22 cell surface marker conjugated to ricin, but do not teach or suggest an onc protein. Further, although, Rybak ('95) and Rybak ('92) disclose Onconase and a chimeric protein comprising an antibody linked to a human pancreatic RNAse, respectively, the references do not describe the particular combination of CD22 antibody with a particular RNase from *Rana pipiens*. Lastly, none of the cited references teach or suggest that the particular combination would be more cytotoxic to B cells than a human RNase conjugated to the same antibody. Indeed, Rybak ('95), in comparing a bovine RNase conjugated to transferrin (or a transferrin antibody) and onconase conjugated to the same moieties, showed little, if any, enhancement of cytotoxicity with the onconase-containing conjugates. Similarly, there is no motivation or suggestion to combine the teachings of the '840 patent with Rybak ('95) or Rybak ('92) to generate onconase-containing reagents that are over 100 times more cytotoxic than the human RNase-containing counterparts.

The additional secondary references, Janeway *et al.* and Huston *et al*, cited for their teachings regarding humanized antibodies, do not cure the deficiencies of the other cited references. Thus, the cited art does not teach or suggest the claimed compositions.

In determining patentability, "secondary considerations are also essential components of the obviousness determination". *See, In re Rouffe*t, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998). The secondary considerations include greater than expected results. *See, e.g.*, MPEP § 716.02, which cites that "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness of the claims at issue." In re Corkill, 711 F.2d 1496 (Fed. Circ. 1985). The data shown in Figures 3 and 5 of the present application demonstrate that LL2-Onconase is about 2,000 times more active than

LL2-EDN. Figure 3 also indicates that LL1-onconase is also surprisingly effective as a B cell cytotoxin in comparison to LL1 conjugated to a human RNase.

A copy of the Declaration made by Dr. Susanna Rybak under 37 CFR §1.132 in parent application 09/071,672 (the Rybak Declaration), provides additional evidence that the invention was not obvious to one of skill at the time the invention was made and further demonstrates the surprising properties of the claimed immunoconjugates.

The data presented in the specification demonstrated that LL2-ONCONASE® exhibited about 2000-fold greater cytotoxic activity than LL2-EDN. As noted above, in previous studies (Rybak *et al. Tumor Targeting* 1:141-147, 1995) comparing bovine RNase A-containing transferrin immunoconjugates to their onconase-containing counterparts, there was little difference in the relative cytotoxicity of the two reagents. Thus, the markedly enhanced activity of B cell-targeted reagents containing onc, *i.e.*, RNase A from *Rana pipiens*, relative to the reagents containing a human RNase was not predicted by the inventors based on earlier studies.

Additional experiments presented in the Rybak Declaration were performed to show the following: (i) that LL2 conjugated to onc proteins other than ONCONASE® also exhibit markedly enhanced activity and (ii) that an immunoconjugate containing onc linked to an antibody that binds to another B cell marker, CD74, also is surprisingly effective compared to human RNase linked to the same antibody.

The LL2 immunoconjugates that were tested included LL2 conjugated to native onconase (nOnc), LL2 conjugated to the recombinant onc protein rapLR1 (described in U.S. provisional application 60/079,751 and incorporated by reference in the present application), LL2 conjugated to [Met-(-1)]rOnc (described in PCT Application No: PCT/US97/02588, which is incorporated by reference in the present application) as well as LL2 conjugated to recombinant human EDN (rhEDN) or recombinant human pancreatic RNase (rhpanc). LL2-[Met-(-1)]rOnc is a control conjugate contining an enzymatically inactive recombinant onconase.

The cytotoxic activity of LL1 immunoconjugates was also further evaluated to supplement the data presented in Figure 3. LL1 is an IgG1 that specifically bind to the Ii subunit of immature MHC Class II antigens (CD74) and, like CD22, is expressed on human B cells. LL1, also like LL2, is rapidly internalized and catabolized by human B-cell lymphomas (Hansen *et al., Biochem. J.* 320:293-300, 1996 and Shih *et al., Int. J. Cancer* 56:528-545, 1994). The LL1 mmuno-conjugates that were tested contained LL1 joined to native onconase and LL1 joined to recombinant human EDN.

The data in Table 1 of the Rybak Declaration demonstrate that reagents containing the recombinant onconase rapLR1 exhibit the same markedly enhanced cytotoxic activity relative to conjugates containing human RNase that was observed with reagents made with the native onconase.

Similarly, the results in Table 1 show that the IC_{50}, the concentration of test sample that inhibits protein synthesis by 50%, is over 100 times greater for the LL1-human RNase conjugate relative to the LL1-nOnc conjugate. The control conjugate containing [Met-(-1)]rOnc], which is a recombinant native onconase expressed in bacteria that is inactive because the amino terminal is not translationally processed, did no exhibit enhanced activity relative to the human RNase-containing conjugates. Thus, LL1-nOnc is over 100 times more effective as a cytotoxic agent relative to the LL1 conjugate made with human RNase.

Dr. Rybak, who has many years of experience in this field, did not predict that the LL2-onc reagent would exhibit cytotoxicity that is over three orders of magnitude greater than that of the LL2-EDN reagent. Similarly, onconase linked to the LL1 antibody, which recognizes the CD74 B cell surface marker, was over 100 times more effective compared to human RNase EDN linked to LL1.

Thus, for the reasons explained above, the superior B-cell cytotoxic activity of onc proteins linked to antibodies to B cell markers was not predictable based on experience in the field, nor was it specifically suggested by teachings in the prior art,

either alone or in combination. Accordingly, the present invention is nonobvious over the prior art. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Appendix A

Currently pending claims

1. (previously amended) A selective cytotoxic reagent comprising an onc protein having measurable ribonucleolytic activity covalently linked to an antibody directed against a surface marker specific to a B cell, wherein the cytotoxic reagent is at least 100 times more cytotoxic to target cells bearing a B cell marker than a comparison reagent comprised of the same antibody joined to the human non-toxic RNase eosinophil-derived neurotoxin (EDN).

2. The reagent of claim 1, wherein the onc protein has the amino acid sequence of SEQ ID NO:1.

3. The reagent of claim 1, wherein the onc protein is produced by recombinant means.

4. The reagent of claim 3, wherein the onc protein has the amino acid sequence of SEQ ID NO:3

5. The reagent of claim 3, wherein the onc protein is encoded by the nucleic acid molecule identified as SEQ ID NO:2.

6. The reagent of claim 1, wherein the antibody is a monoclonal antibody.

7. The reagent of claim 6, wherein the monoclonal antibody is humanized.

8. The reagent of claim 7, wherein the monoclonal antibody is a single chain antibody.

9. The reagent of claim 1, wherein the antibody is specific for B cell lymphomas.

10. The reagent of claim 9, wherein the antibody is selected from the group consisting of RFB4 and LL2.

11. The reagent of claim 1, wherein the surface marker is CD22.

12. The reagent of claim 1, wherein the surface marker is CD74.

13. (cancelled)

14. The reagent of claim 1, wherein the onc protein is conjugated to the antibody through recombinant fusion.

15. withdrawn from examination

16. A pharmaceutical composition comprising a selective cytotoxic reagent comprising an onc protein having measurable ribonucleolytic activity joined to an antibody directed against a cell surface marker specific to a B cell together with a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein the onc protein has the amino acid sequence of SEQ ID NO:1.

18. The pharmaceutical composition of claim 16, wherein the onc protein is produced by recombinant means.

19. The pharmaceutical composition of claim 18, wherein the onc protein has the amino acid sequence of SEQ ID NO:3.

20. The pharmaceutical composition of claim 18, wherein the onc protein is encoded by the nucleic acid molecule identified as SEQ ID NO:2.

21. The pharmaceutical composition of claim 16, wherein the onc protein is conjugated to the antibody through recombinant means.

22. The pharmaceutical composition of claim 16, wherein the antibody is a monoclonal antibody.

23. The pharmaceutical composition of claim 22, wherein the monoclonal antibody is humanized.

24. The pharmaceutical composition of claim 23, wherein the monoclonal antibody is a single chain antibody.

25. The pharmaceutical composition of claim 16, wherein the antibody is directed against a surface marker present on B cell lymphomas.

26. (previously amended) The pharmaceutical composition of claim 25, wherein the antibody is selected from the group consisting of RFB4 and LL2.

27.-34. previously cancelled